REMARKS

Claims 61-63, 65-68, 77, 79-81, 86, 87, 91, 93-101 and 104-115 were pending. Claims 96-100 were previously withdrawn. Claims 1, 87 and 95 have been amended. Thus, upon entry of this amendment, claims 61-63, 65-68, 77, 79-81, 86, 87, 91, 93-101 and 104-115 will remain pending in the application.

Support for the amendments to the claims and the new claims may be found in the specification and claims as originally filed. Specifically, support for the amendments to claim 1 may be found at least at page 6, lines 9-11, page 27, lines 4-8 and page 37, lines 1-2 of the specification, as filed. Support for the amendments to claim 87 may be found at least at page 18, lines 4-13 of the specification, as filed. Claim 95 has been amended to correct its dependency. No new matter has been added.

The foregoing claim amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in this or in any former Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicants respectfully submit that the claims are now in condition for allowance.

Interview

Applicants and their Attorney thank the Examiner for the courtesy of the November 20, 2008 interview at the U.S. Patent and Trademark Office during which the foregoing claim amendments and outstanding rejections were discussed. The following remarks are supplemental to the remarks previously made of record.

Further Response to the Rejection of Claims Under Section 102(b) in view of Hamada et al.

The Examiner previously rejected claims 61, 62, 65-67, 81, 86, 87 and 93 under §102(b) as being anticipated by Hamada *et al.* in light of Roitt *et al.* This rejection is respectfully traversed.

The claims, as amended, are directed to compositions comprising an amount of ***an isolated monoclonal antibody*** effective to prevent staphylococcal infection in neonates and a pharmaceutically acceptable carrier, wherein the antibody specifically binds to poly-glycerol phosphate of Lipoteichoic acid (LTA) of Gram positive bacteria and is of the IgG isotype, wherein the antibody binds to and ***enhances opsonization*** of multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans* by phagocytic cells with or without complement as compared to an appropriate control in an in vitro opsonization assay.

The Examiner has stated that the 3G6 antibody disclosed by Hamada *et al.* would inherently opsonize gram positive bacteria in light of the teaching of Roitt. The Examiner relies on Roitt as teaching that "antibodies inherently have the ability to opsonize bacteria by virtue of their binding...to a large extent as compare [sic] to the absence of any opsonin (see page 16 of the Office Action dated February 23, 2007).

Under principles of inherency, "if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates [the claim]." *Mehl/Biophile Int'l Corp. v. Milagraum,*192 F.3d 1362, 1365 (Fed Cir. 1999). To show that the prior art "necessarily" functions in accordance with, or includes the claimed limitations, one must show more than a mere probability or possibility of the inherent feature's existence. *See SmithKline Beecham Corp. v. Apotex Inc.,* 403 F.3d 1331, 1346 (Fed. Cir. 2005). Therefore, "[i]nherency...***may not be established by probabilities or possibilities***. The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Mehl/Biophile,* 192 F.3d 1362 at 1365 (emphasis added) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939)). Additionally, MPEP § 2112 requires that

> "[i]n relying on the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. Appl. & Inter. 1990) (emphasis in original).

Moreover, a prima facie case [of inherency] can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Applicants respectfully submit that the data and literature support that it is the properties of an isolated antibody, itself, that determine whether an antibody is opsonic and that Applicants have submitted evidence showing that the prior art antibodies do not necessarily possess the properties set forth in the pending claims.

More specifically, as set forth in the Amendment and Response dated September 9, 2008, the Patent Office has not provided sufficient reasoning to establish that the antibody described by Hamada *et al.* necessarily possesses the characteristics of the claimed antibodies. As set forth in that Amendment and Response, the ability of an antibody to opsonize correlates with its ability to be protective. Importantly, not all anti-LTA antibodies are opsonic. The fact that the antibody described by Hamada *et al.* does not agglutinate multiple serotypes of Staphylococcus, including *Staphylococcus aureus*, indicates that the antibody would likely not be opsonic. Moreover, the heterogeneity in functional activity (agglutination) displayed by the 3G6 antibody clearly indicates that the antibody is not appropriate for therapeutic use, *e.g.*, for preventing staphylococcal infections in neonates, as required by the claims. Applicants' additional arguments are set forth below.

To begin with, Applicants respectfully point out that Hamada *et al.* do not demonstrate agglutination or binding of bacteria by the 3G6 antibody as suggested by the Examiner, as the 3G6 antibody was not isolated and purified in these assays, but rather was included in ascitic fluid. Specifically, Hamada *et al.* performed agglutination and ELISA experiments with whole bacteria using mouse ascites fluid which contained 3G6 antibodies (see, *e.g.*, footnotes (a) and (b) of Table 3 of Hamada *et al.*). The Encyclopedia of Medical Biology[1] defines ascites fluid as "***[p]eritoneal exudate*** which includes fluid and inflammatory cells" and that

> [i]n experimental animals, ascites may be produced in response to plasmacytoma or hybridoma cells growing in the abdominal cavity. A single mouse may produce up to 10ml of ascitic fluid, which can be tapped off with a syringe and which can contain 1-10mg ml^{-1} of a monoclonal antibody. Repeated injections of

[1] A copy of which is attached herein as Appendix A.

> complete Freund's adjuvant may also be used to induce ascites. The fluid will contain approximately the same level of antibody as the animal's own serum. This may be used as a source of polyclonal immunoglobulin since the induction of ascites can be timed to coincide with elevated levels of specific antibodies following immunization.

Mouse ascites fluid, or peritoneal exudate, from mice inoculated with hybridoma cells contains many components besides the antibody produced by that hybridoma, including for example, opsonins, complement, lectins, aggultinins, as well as antibodies of multiple specificities including those with binding activity to bacteria. Accordingly, there are numerous components present in the mouse ascites fluid tested by Hamada *et al.,* only one of which is the 3G6 antibody. Hamada *et al.* do not in fact demonstrate that it is the 3G6 antibody, itself, which is the component of the mouse ascites fluid which leads to agglutination and binding of bacteria. Indeed, other components, or combinations of components of the ascites fluid could be responsible for these effects, or could act in concert with the 3G6 antibody to produce the desired effect (see, *e.g.,* Reider *et al.*,[2] which discusses the bactericidal activity of normal ascitic fluid, which mediates opsonization independent of specific antibodies).

In addition, Clark and Easmon[3] report that antibody alone is often not opsonic, and may require peritoneal fluid components in order to be opsonic. Specifically, Clark and Easmon report that intravenous immunoglobulin (IVIG) preparations showed ***no opsonic activity*** against *S. epidermidis* alone. However, when IVIG was mixed with human peritoneal dialysis fluid, which is equivalent to mouse ascites fluid, good opsonic activity resulted (see, *e.g.,* Abstract of Clark and Easmon). Clark and Easmon explain that "[t]his was probably due to the presence of low concentrations of C3 [complement] in the [peritoneal dialysis] effluent" and that "opsonization resulted from ***a combination of the high IgG concentration and low complement*** value" (see, *e.g.,* Abstract and page 860, second full paragraph of Clark and Easmon). Thus, Clark and Easmon demonstrate that it was not the immunoglobulin which provided the opsonic activity, but rather the ***combination*** of the immunoglobulin with complement components found in human peritoneal dialysis fluid.

Accordingly, as human peritoneal fluid and mouse ascitic fluid contain numerous components besides antibodies, one of ordinary skill in the art would not reasonably conclude

[2] A copy of which is attached herein as Appendix B.
[3] Clark and Easmon was previously submitted as Appendix H in the Amendment and Response filed September 9, 2008.

based on the teachings of Hamada *et al.* that the 3G6 antibody, itself, has the characteristics of agglutination and binding of bacteria. Indeed, as evidenced by Clark and Easmon, it is likely that it is the ***combination*** of the mouse ascitic fluid and the 3G6 antibody, and not the antibody, itself, that results in the aggultination shown in Table 3 of Hamada *et al.* Accordingly, there is no evidence in any of the cited art that the 3G6 antibody has the ability to agglutinate and bind bacteria by itself, nor has it been shown to have opsonic activity.

Therefore, Applicants respectfully submit that it is the properties of an isolated antibody, itself, that determine whether an antibody is opsonic, and that there is no teaching or suggestion in any of the cited art that reasonably supports a determination that the 3G6 antibody, itself, necessarily possesses the characteristics of the presently claimed antibodies. As such, the Examiner is respectfully requested to reconsider and withdraw the rejection based on the inherent characteristics of the 3G6 antibody of Hamada *et al.*

Furthermore, Applicants reiterate that regardless of what substance in the ascites fluid is responsible for the data presented in Table 3 of Hamada *et al.,* the data of Table 3 indicate that the 3G6 antibody is not appropriate for therapeutic use, *e.g.,* for preventing staphylococcal infections in neonates, as required by the pending claims. As discussed during the Examiner interview, the instant invention is ***not*** directed to developing ***active immunity***, *i.e.,* generating an immune response to antigen in a subject. Rather, the invention is directed to the use of preformed, isolated monoclonal antibodies which are specific for LTA, and which have certain properties that make them protective, to prevent infection in neonates. These antibodies are ***passively*** administered to a neonate and function to prevent infection, and have been demonstrated to be effective *in vivo* in the application as filed.

In particular, the specification demonstrates that an isolated anti-LTA monoclonal antibody, 96-110, an antibody within the scope of the claims, increased survival in ***immune deficient*** suckling rat models after infection with both lethal coagulase positive and coagulase negative staphylococci. In an experiment shown in Example 3, the 96-110 monoclonal antibody was administered to immunocompromised suckling rats 30 minutes before and 24 and 48 hours after infection with *S. aureus*, resulting in enhanced opsonic activity of bacteria and increased survival of the animals. In a second experiment in the same animal model described in Example 13 of the specification, a chimeric form of the 96-110 antibody, administered 30 minutes before and 24 hours after infection, was opsonic, enhanced survival against multiple strains of *S.*

epidermidis, and promoted clearance of the staphylococci from the blood. Thus, the specification clearly demonstrates that antibodies with the characteristics of the claimed invention are effective *in vivo* against both coagulase positive and coagulase negative staphylococci in immunocompromised subjects lacking normal immune components.

Furthermore, antibodies with the characteristics of the claimed invention have been shown to be efficacious in human neonates.[4] In contrast, other clinical efforts using anti-staphylococcal antibodies have failed to produce antibodies which effectively prevent infection in neonates.[5]

Therefore, in view of the foregoing, there is no evidence that the prior art cited antibodies necessarily possess the characteristics of the claimed isolated antibodies. None of the cited art explicitly or inherently teaches or suggests isolated monoclonal antibodies which bind to and enhance opsonization of multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans* by phagocytic cells or prevent infection in animal models or human beings. As the evidence of record fails to reasonably support a determination that the prior art antibodies necessarily possess the characteristics of the claimed antibodies, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

[4] Weisman, a copy of which is attached herein as Appendix C, provides a review of several anti-staphylococcal antibodies, including an antibody having the characteristics as claimed, the 96-110 chimeric antibody, also known as Pagibaximab®.

[5] See, *e.g.,* DeJonge *et al.,* a copy of which is attached herein as Appendix D, which demonstrates that IHN-A21 antibodies with specificity for Staphylococci did not reduce the frequence of human neonatal infection.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400. Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. SYNI-003CN from which the undersigned is authorized to draw.

Dated: December 3, 2008

Respectfully submitted,

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